Recent Advances in Radiation Therapy in Hodgkin's Lymphoma
Introduction

- Hodgkin's Lymphoma described in 1832 by Dr Thomas Hodgkin
- Believed to be of B cell origin
- Reed Sternberg cell is the neoplastic cell
- Derived from the germinal cell of lymph nodes
Historical Perspective

- The evolution of megavoltage radiation therapy closely linked to the treatment of Hodgkin's Lymphoma.
- Magna field radiation resulted in unprecedented outcomes as reported by Kaplan et al.

Long-Term Results of Palliative and Radical Radiotherapy for Hodgkin's Disease Henry S. Kaplan Cancer Res 1966;26:125
Historical Perspective..

- The introduction of Nitrogen mustard saw the introduction of one of the first RCTs in oncology
- The MOPP regimen proved its worth as the first combination chemotherapy agent
- ABVD found to be similar in efficacy as MOPP
BBCl Experience

- Between 2010 - 2011 16 patients registered (0.30% of total)
- Male : Female ratio : 11:5 (2.2)
- 40 patients identified registered between 2009-2011
  - Files retrieved : 26
  - Hodgkin's disease: 22
  - Took treatment: 18
BBCI Experience

- Median age: 20 Years (7 – 77 years)
- 13 patients received RT (IFRT)
- All patients had received ABVD (2-6 cycles)
- IFRT dose ranged from 20 - 46 Gy
- Cervical and mediastinal RT most commonly given
- Outcome data: Immature and incomplete but patients post CCT+RT (7) who came for followup are having CR
New Developments in RT

- When to give?
- How much to give?
- How to give?
Selection of Treatment

Complete Staging Workup

CS I - II → CS III-IV

Risk Grouping

Risk Grouping ?
# Risk Grouping Stage I-II

<table>
<thead>
<tr>
<th>Criteria</th>
<th>NCIC-C</th>
<th>German HD</th>
<th>EORTC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&gt; 40 Years</td>
<td>&gt; 50 Years</td>
<td>--</td>
</tr>
<tr>
<td>Bulky Mediastinal Disease</td>
<td>--</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>ESR without B symptoms</td>
<td>&lt; 50 mm/hr</td>
<td>&lt; 50 mm/hr without B symptom</td>
<td>&lt; 50 mm/hr without B symptom</td>
</tr>
<tr>
<td>ESR with B symptoms</td>
<td>-</td>
<td>&lt; 30 mm/hr with B symptoms</td>
<td>&lt; 30 mm/hr with B symptoms</td>
</tr>
<tr>
<td>Sites of Involvement</td>
<td>&lt; 3</td>
<td>&lt; 3</td>
<td>&lt; 4</td>
</tr>
<tr>
<td>Histology</td>
<td>LP/NS</td>
<td>--</td>
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</tr>
</tbody>
</table>

Patients considered low risk (NCIC-C) or good prognosis if they have all the above factors.
Stage I-II - CMT

• CMT is used in early stage disease following results from 5 major trials
• All showed equivalent or better results using CMT
• The long term increased risk of SMN finally swung the pendulum towards CMT
Stage I – II CMT

<table>
<thead>
<tr>
<th>Trial</th>
<th>Study Arm</th>
<th>FU</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>SWOG/ CALGB</td>
<td>STNI (36 -40 Gy)</td>
<td>3yr</td>
<td>96%</td>
</tr>
<tr>
<td></td>
<td>AVx3 + STNI (36-40 years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GHSG HD-7</td>
<td>EFRT (30-40 Gy)</td>
<td>5yr</td>
<td>92%</td>
</tr>
<tr>
<td></td>
<td>ABVD + EFRT (30-40 Gy)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Milan</td>
<td>ABVD x 4 + STNI (30 -40 Gy)</td>
<td>12yr</td>
<td>96%</td>
</tr>
<tr>
<td></td>
<td>ABVD x 4 + IFRT (36 -40 Gy)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EORTC H7F</td>
<td>STNI (36-40 Gy)</td>
<td>10yr</td>
<td>92%</td>
</tr>
<tr>
<td></td>
<td>EBVP x 6 + IFRT (36 -40 Gy)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EORTC/GELA H8F</td>
<td>STNI (36 -40 Gy)</td>
<td>10yr</td>
<td>92%</td>
</tr>
<tr>
<td></td>
<td>MOPP/ABV x 3 + IFRT (36-40 Gy)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Stage I-II Good Prognosis

- Seminal trial: German HD10 trial
- 1370 patients – randomized into 4 groups
  - ABVD x4 > IFRT 30 Gy
  - ABVD x2 > IFRT 30 Gy
  - ABVD x4 > IFRT 20 Gy
  - ABVD x2 > IFRT 20 Gy

- Non-inferiority trial design: Difference in Freedom from treatment failure rate < 7% in pooled groups

Reduced Treatment Intensity in Patients with Early-Stage Hodgkin’s Lymphoma Engert et al N Engl J Med 363;7 Aug
Stage I-II Good Prognosis

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Treatment Group</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Group 1: 4xABVD + 30 Gy IFRT (N = 298)</td>
</tr>
<tr>
<td>Survival rate — % (95% CI)‡</td>
<td></td>
</tr>
<tr>
<td>At 5 years</td>
<td></td>
</tr>
<tr>
<td>Overall survival</td>
<td>96.9 (94.2–98.4)</td>
</tr>
<tr>
<td>Freedom from treatment failure</td>
<td>92.8 (89.1–95.3)</td>
</tr>
<tr>
<td>Progression-free survival</td>
<td>93.9 (90.3–96.2)</td>
</tr>
<tr>
<td>At 8 years</td>
<td></td>
</tr>
<tr>
<td>Overall survival</td>
<td>94.4 (90.2–96.8)</td>
</tr>
<tr>
<td>Freedom from treatment failure</td>
<td>87.2 (81.3–91.4)</td>
</tr>
<tr>
<td>Progression-free survival</td>
<td>88.4 (82.6–92.4)</td>
</tr>
</tbody>
</table>
Stage I-II Good Prognosis

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Chemotherapy Comparison</th>
<th>Radiation Therapy Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Groups 1 and 2 (N=596)</td>
<td>Groups 3 and 4 (N=594)</td>
</tr>
<tr>
<td>Survival rate — % (95% CI)‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 5 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall survival</td>
<td>97.1 (95.4–98.2)</td>
<td>96.6 (94.7–97.8)</td>
</tr>
<tr>
<td>Freedom from treatment failure</td>
<td>93.0 (90.5–94.8)</td>
<td>91.1 (88.3–93.2)</td>
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<td>Progression-free survival</td>
<td>93.5 (91.1–95.3)</td>
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<td>At 8 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall survival</td>
<td>94.6 (92.0–96.4)</td>
<td>94.4 (91.9–96.1)</td>
</tr>
<tr>
<td>Freedom from treatment failure</td>
<td>88.4 (84.8–91.3)</td>
<td>85.7 (81.8–88.9)</td>
</tr>
<tr>
<td>Progression-free survival</td>
<td>89.1 (85.5–91.8)</td>
<td>86.0 (82.1–89.1)</td>
</tr>
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94.9 (92.2–96.6) 95.6 (93.2–97.1)
Stage I-II Good Prognosis

- Present standard of care for early stage I-II good prognosis / low risk disease is:
  - ABVD x 2 cycles
  - IFRT 20 Gy
- Reduces acute toxicity by almost 50%
- Presently results till 10 years.
Stage I-II Good Prognosis

- Can we omit RT and replace by CCT alone?
- Unfortunately no ABVD containing trials!! (Two trials of older era employed STNI not IFRT)

EORTC/GELAH9F:

- EBVP x 6 + IFRT 36 Gy
- EBVP x 6 + IFRT 20 Gy
- EBVP x 6

Patients randomized after CR to EBVP x 6
Stage I-II: Good Prognosis

- Despite CR to EBVP the 5 year RFS in no RT arm was 70% vs 86 - 89% in the RT arms.
- Arm discontinued as met stopping rules (1 - $\beta$ was kept at 77%).
- All relapsed at involved sites.
- Thus EBVP x 6 followed by even a CR is not an indication for omitting RT.
Stage I-II Poor Prognosis

- This group includes patients with:
  - Bulky disease
  - Age > 50
  - B symptoms
  - > 3 – 4 sites of involvement
  - Extranodal involvement
  - Elevated ESR

- Any one of the factors is enough
Stage I-II Poor Prognosis

- German HD11 trial
- 2 x 2 factorial design 1395 patients

Groups:
  - ABVD x 4 + **IFRT (30 Gy)**
  - ABVD x 4 + **IFRT (20 Gy)**
  - BEACOPP x 4 + **IFRT (30 Gy)**
  - BEACOPP x 4 + **IFRT (20 Gy)**
Stage I-II: Poor Prognosis

<table>
<thead>
<tr>
<th>Arm</th>
<th>5 Year FFTF</th>
<th>5 Year OS</th>
</tr>
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<tbody>
<tr>
<td>ABVD x 4 + 30 Gy</td>
<td>85.3%</td>
<td>94.3%</td>
</tr>
<tr>
<td>BEACOPP x 4 + 30 Gy</td>
<td>87.0%</td>
<td>94.6%</td>
</tr>
<tr>
<td>ABVD x 4 + 20 Gy</td>
<td>81.1%</td>
<td>95.1%</td>
</tr>
<tr>
<td>BEACOPP x 4 + 20 Gy</td>
<td>86.8%</td>
<td>93.8%</td>
</tr>
</tbody>
</table>
Stage I – II: Poor Prognosis

Important Conclusions (HD 11):

- ABVD x 4 followed by IFRT 20 Gy is suboptimal in terms of freedom from treatment failure and PFS
- ABVD x 4 followed by IFRT 30 Gy is equivalent to BEACOPP arms (with IFRT 20 Gy or 30 Gy)
- BEACOPP results in acute toxicity in 70% compared with 50% in ABVD
- 30 Gy IFRT also was more toxic (12% vs 6%) than 20 Gy.
Stage I-II Poor Prognosis

- The EORTC/GELA H9 U trial compared 3 regimens:
  - ABVD x 4 + IFRT 30 Gy
  - ABVD x 6 + IFRT 30 Gy
  - BEACOPP x 4 + IFRT 30 Gy
- The cancer related outcomes were similar in 3 arms
- IFRT 30 Gy after ABVD 4 – 6 cycles is thus considered standard
Stage III- IV

- The only positive study that supports the role of RT from TMH
- Included population: Heterogenous mainly bulky MC disease (more representative of Indian scenario?)
- The TMH study did show an improved OS if IFRT was added after 6 cycles of ABVD (89% vs 76%)
Stage III - IV

- Results from other studies including interim results from the HD 12 show that addition of RT adds little in terms of benefit.
- However HD12 employed escalated BEACOPP not ABVD.
- The HD 15 trial therefore employed RT in a selected population:
  - Residual Node > 2.5 cm
  - Positive PETCT
- In this group IFRT to 30 Gy resulted in 1 year PFS of 85% in a validation PETCT based cohort.
Radiation Volume

• As the dose has reduced so have the volumes

• Some Definitions:
  • TNI : Total Nodal Radiation
  • STNI : Subtotal Nodal Radiation
  • EFRT : Extended Field Radiation
  • IFRT : Involved Field Radiation
  • INRT : Involved Nodal Radiation
Radiation Volume: TNI

Total Nodal Irradiation
Radiation Volume: STNI

Subtotal Nodal Irradiation
Radiation Volume: EFRT

Extended Field Radiation
Radiation Volume: IFRT

Involved Field Radiation
Radiation Volume: INRT

Involved Nodal Radiation
Involved Nodal Radiation

- Presently being evaluated in EORTC-GELA lymphoma trial
- Concept based on the finding that site of relapse is the initial node.

Requirements for Implementation:
- Rad Onc must see patient at initial evaluation
- Full planning CT scan
- If PET CT done pre-chemotherapy then it should also be done in planning position
  Original Nodal volume is the CTV.
Involved Nodal Radiation

Prechemo

Post Chemo

Fusion
Delivery Improvements

- CT based planning now considered de rigueur in many western institutes
- Treatment planning studies have shown even further reductions in OAR doses using IMRT
- Important consideration in treating mediastinal HD.
- Proton therapy can help in further reductions in dose.
Delivery Improvements
Conclusions

● Radiation still a part of treatment modality in EHD.

● Volumes progressively reducing.

● Doses reduced to 20 Gy for favourable EHD and 30 Gy for unfavourable.

● Role in advanced stage HD likely to be increasingly determined by post chemo PET results.

● Reduction in long term morbidity to be expected but not proven.
Questions ?